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(FILE 'HOME' ENTERED AT 09:46:42 ON 19 MAY 2000)

FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 09:46:56 ON 19 MAY 2000

L1 58 S ((LINDHOFER H.) OR (LINDHOFER H) OR (LINDHOFER, HORST) OR  
(LI  
L2 2128 S ((KOLB H.) OR (KOLB H.-J.) OR (KOLB H) OR (KOLB H-J) OR  
(KOLB  
L3 119 S ((ZEIDLER R.) OR (ZEIDLER R) OR (ZEIDLER, REINHARD) OR  
(ZEIDL  
L4 52 S ((BORNKAMM G.) OR (BORNKAMM G) OR (BORNKAMM, GEORG) OR  
(BORNK  
L5 0 S L1 AND L2 AND L3 AND L4  
L6 3663 S BISPECIFIC OR TRISPECIFIC  
L7 44 S L6 AND (L1 OR L2 OR L3 OR L4)  
L8 25 DUP REM L7 (19 DUPLICATES REMOVED)  
L9 5 S EX VIVO IMMUNIZATION  
L10 2 DUP REM L9 (3 DUPLICATES REMOVED)  
L11 8202 S PASSIVE IMMUNI?  
L12 3 S L11 AND L6  
L13 3 DUP REM L12 (0 DUPLICATES REMOVED)  
L14 4045 S CELL? VACCIN?  
L15 16 S L14 AND L6  
L16 8 DUP REM L15 (8 DUPLICATES REMOVED)

L16 ANSWER 1 OF 8 MEDLINE DUPLICATE 1

ACCESSION NUMBER: 1998192213 MEDLINE

DOCUMENT NUMBER: 98192213

TITLE: \*\*\*Bispecific\*\*\* antibodies increase T-cell  
stimulatory

capacity in vitro of human autologous virus-modified tumor  
vaccine.

AUTHOR: Haas C; Strauss G; Moldenhauer G; Iorio R M; Schirmacher  
V

CORPORATE SOURCE: Division of Cellular Immunology, German Cancer Research  
Center, Heidelberg.

SOURCE: CLINICAL CANCER RESEARCH, (1998 Mar) 4 (3) 721-30.  
Journal code: C2H. ISSN: 1078-0432.

PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199807

ENTRY WEEK: 19980705

AB The production and functional testing of two new \*\*\*bispecific\*\*\*  
(bs)

hybrid antibodies [Abs; bs Ab hemagglutinin-neuraminidase (HN) x CD3 and  
bs Ab HN x CD28] designed for cancer vaccine modification are described.  
They allow distinct modifications of the human tumor \*\*\*cell\*\*\*

\*\*\*vaccine\*\*\* ATV-NDV, an autologous tumor \*\*\*cell\*\*\*

\*\*\*vaccine\*\*\* already modified by infection with Newcastle disease  
virus. The bs Abs use the viral HN molecule as a common foreign anchoring  
molecule for attachment to the tumor cells and allow the introduction of  
anti-CD3 or anti-CD28 T-cell-stimulatory molecules. The bs Abs attached

to

tumor target cells were able to cross-link CTL effector cells and  
up-regulate T-cell activation markers on autologous cancer patient-

derived

CD4 and CD8 T lymphocytes. This strategy of combining a \*\*\*cellular\*\*\*  
\*\*\*vaccine\*\*\* with a bs Ab is highly specific, quick, and economical  
and  
has broad-range applications. Five ng or less of target cell-bound bs Ab  
HN x CD28 were effective at augmenting T-cell-mediated antitumor  
cytotoxicity.

L16 ANSWER 2 OF 8 MEDLINE DUPLICATE 2  
ACCESSION NUMBER: 1999081280 MEDLINE  
DOCUMENT NUMBER: 99081280  
TITLE: Immunization with virus-modified tumor cells.  
AUTHOR: Schirmacher V; Ahlert T; Probstle T; Steiner H H;  
Herold-Mende C; Gerhards R; Hagmuller E; Steiner H H  
CORPORATE SOURCE: Abteilung Zellulare Immunologie (G0100), Deutsches  
Krebsforschungszentrum, Heidelberg, Germany.  
SOURCE: SEMINARS IN ONCOLOGY, (1998 Dec) 25 (6) 677-96. Ref: 66  
Journal code: UN5. ISSN: 0093-7754.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals; Cancer Journals  
ENTRY MONTH: 199903  
ENTRY WEEK: 19990303

AB Direct infection of tumor cells with viruses transferring protective or  
therapeutic genes-a frequently used procedure for production of tumor  
vaccines in human gene therapy-is often limited by the number of tumor  
cells that can reliably be infected, as well as by issues of selectivity  
and safety. In this review, we describe an efficient, selective, and safe  
way of infecting human tumor cells with a natural virus with interesting  
pleiotropic immune stimulatory properties, the avian paramyxovirus  
Newcastle disease virus (NDV). Advantages of this virus are its good  
cell-binding properties, its selective replication in tumor cell  
cytoplasm, which is independent of cell proliferation, and its relative  
safety. Most important for its use as an adjuvant in human cancer vaccine  
are its ability to introduce T-cell costimulatory activity, to prevent  
anergy induction, and to induce locally chemokines (eg, RANTES, IP-10)

and  
cytokines (eg, interferon alpha, beta [IFN-alpha, beta] and tumor  
necrosis  
factor-alpha [TNFalpha]) that affect T-cell recruitment and activation. A  
further development consists of attachment-via NDV-derived  
hemagglutinin-neuraminidase (HN) membrane-anchoring molecules-of  
universal  
defined \*\*\*bispecific\*\*\* reagents such as T-cell-activating anti-CD28  
antibodies. Finally, we summarize the status of our clinical studies with  
the autologous virus modified live \*\*\*cell\*\*\* \*\*\*vaccine\*\*\*  
(ATV)-NDV.

L16 ANSWER 3 OF 8 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.DUPLICATE 3  
ACCESSION NUMBER: 1998404443 EMBASE  
TITLE: Modification of cancer vaccines by virus infection and  
attachment of \*\*\*bispecific\*\*\* antibodies: An  
effective  
alternative to somatic gene therapy.  
AUTHOR: Schirmacher V.; Haas C.  
CORPORATE SOURCE: V. Schirmacher, German Cancer Research Center, Division  
of

SOURCE: Cellular Immunology, Im Neuenheimer Feld 280, D-69120  
Heidelberg, Germany. V.Schirmacher@DKFZ-Heidelberg.de  
Advances in Experimental Medicine and Biology, (1998)  
451/-

(251-257).  
Refs: 43  
ISSN: 0065-2598 CODEN: AEMBAP  
COUNTRY: United States  
DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 016 Cancer  
026 Immunology, Serology and Transplantation  
037 Drug Literature Index  
LANGUAGE: English  
SUMMARY LANGUAGE: English

AB A new type of cancer vaccine for therapeutic application in cancer patients is described. It consists of three components: 1) Autologous tumor cells, 2) Newcastle Disease Virus to be used for infection and 3) \*\*\*bispecific\*\*\* antibodies (bsAb) which attach to the viral hemagglutinin neuraminidase (HN) molecule on the infected tumor cells. A standardized procedure has been developed for generating virus infected human autologous tumor \*\*\*cell\*\*\* \*\*\*vaccines\*\*\* (ATV-NDV) which includes cell dissociation removal of leukocytes and cell debris, .gamma.-irradiation and cryopreservation. Modification with the non-virulent strain NDV-Ulster is performed within 30 minutes of co-incubation. Virus infection potentiated tumor vaccine T cell stimulatory capacity and created a vaccine which has been successful in mouse tumor models in preventing or delaying metastatic spread and improving survival. Virus potentiation required cell surface binding but not infection. Clinical phase II studies in patients with breast or ovarian cancer suggest clinical effectivity of postoperative vaccination with a high quality of ATV-NDV vaccine. Tumor cell number and viability turned out to be statistically significant parameters for quality and efficacy. While virus infection already increased immunogenicity of the tumor vaccine, further augmentation of T cell stimulatory capacity is achieved by attachment of specially designed \*\*\*bispecific\*\*\* antibodies bsAb HN x CD28 or bsAb HN x CD3. In human T cell stimulation studies in vitro, the bsAb-vaccine caused upregulation of early and late  
T cell activation markers, stimulated T cell proliferation and induced cell mediated cytotoxicity and tumor cytostasis in non-modified bystander tumor cells. This tumor vaccine modification procedure is highly specific, quick and economic and has broad range clinical applications.

L16 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1997:761947 CAPLUS  
DOCUMENT NUMBER: 128:33765  
TITLE: New antigen presenting cells, a process for preparing the same and their use as \*\*\*cellular\*\*\*  
\*\*\*vaccines\*\*\*  
INVENTOR(S): Chokri, Mohamed; Bartholeyns, Jacques; Romet-Lemonne, Jean Loup  
PATENT ASSIGNEE(S): I.D.M. Immuno-Designed Molecules, Fr.  
SOURCE: Eur. Pat. Appl., 18 pp.  
CODEN: EPXXDW  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 808897	A1	19971126	EP 1996-401099	19960521
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
CA 2252505	AA	19971127	CA 1997-2252505	19970515
WO 9744441	A1	19971127	WO 1997-EP2703	19970515
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9729615	A1	19971209	AU 1997-29615	19970515
EP 925356	A1	19990630	EP 1997-924012	19970515
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000503545	T2	20000328	JP 1997-541583	19970515
PRIORITY APPLN. INFO.:				
			EP 1996-401099	19960521
			WO 1997-EP2703	19970515
AB	The invention relates to macrophages characterized in that they have the following properties: they present on their surface : antigen CD14 with a mean intensity of about 20 to about 200, antigen CD64 with a mean intensity of about 20 to about 200. They are substantially devoid of the surface antigens CD1a and CD1c. The presence and mean intensities resp. of CD14, CD64 and the absence of CD1a and CD1c being for instance detd.			
by	immunofluorescence staining and flow cytometry anal. They present a phagocytosis property such as detd. by the following test: said phagocytosis capacity being evaluated by an uptake of formalin fixed yeast, for example, by culturing macrophages for 2 h, adding yeast in			
1/10	macrophages/yeast ratio and incubating at 37.degree.C, 5% CO2 atmosphere for 2-3 h fixing by the May-Grunwald-Giems a (MGG) staining, and the percentage of phagocytic macrophages being quantified for instance by microscopic anal.. They have the property of stimulating the proliferation of allogenic lymphocytes such as detd. by the following			
test	: allogenic primary mixed lymphocytes reaction (MLR) was carried out in 96-well microtiter plates by adding different nos. (2x103 to 2x105 in 100 .mu.l medium/well) of macrophages to 2x105 in 100 .mu.l medium/well of allogenic T cells purified from buffy coats and after 5 days incubation			
at	37.degree.C. Cell proliferation was assessed by a colorimetric method, such as the hydrolysis of tetrazolium salt WST-1 (Boehringer Mannheim, Germany ), (slightly red) to formazan (dark Red).			
L16	ANSWER 5 OF 8 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.DUPLICATE 4			
ACCESSION NUMBER:	97315620 EMBASE			
DOCUMENT NUMBER:	1997315620			
TITLE:	Effective introduction of T cell costimulatory molecules into virus modified tumor ***cell*** ***vaccines*** by modification with ***bispecific*** antibodies.			
AUTHOR:	Haas C.; Schirmacher V.			
CORPORATE SOURCE:	Prof. V. Schirmacher, Deutsches Krebsforschungszentrum, Abteilung 0710, Im Neuenheimer Feld 280, D-69120 Heidelberg, Germany			

SOURCE: International Journal of Oncology, (1997) 11/5 (951-957).  
Refs: 35  
ISSN: 1019-6439 CODEN: IJONES

COUNTRY: Greece  
DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 016 Cancer  
026 Immunology, Serology and Transplantation  
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB This report describes the generation of \*\*\*bispecific\*\*\* antibodies which bind with one arm to virus modified tumor \*\*\*cell\*\*\* and introduce with the other arm anti-murine CD28 T cell

costimulatory molecules. This is an effective alternative to somatic gene therapy strategies using genes coding for ligands of CD28 such as CD80 (B7-1) or CD86 (B7-2). While these B7 molecules interact not only with CD28 but also with CLTA-4, thereby generating a negative signal, agonistic

anti CD28 antibodies only bind to CD28 and therefore deliver only positive

costimulatory signals. The new \*\*\*bispecific\*\*\* antibody (bsAb) HN x CD28 allows the introduction of anti-CD28 antibodies into the tumor \*\*\*cell\*\*\* \*\*\*vaccine\*\*\* ATV-NDV, an autologous tumor

\*\*\*cell\*\*\*  
\*\*\*vaccine\*\*\* already modified by infection with Newcastle Disease

Virus (NDV). The bsAb HN x CD28 attaches with its anti-HN binding site to the NDV derived hemagglutinin-neuraminidase (HN) molecule which serves as a common foreign anchoring molecule in the vaccine. NDV infected tumor

cells which were further modified with HN x CD28 on their cell surface (bs-vaccine), showed increased T cell stimulatory capacity in vitro. This was revealed by augmented proliferation as well as augmented CTL activity.

When syngeneic mice were injected with aggressive murine ESb lymphoma cells which were infected with NDV and further modified with the bsAb HN

x  
CD28, delayed tumor development and prolonged survival was observed in comparison to respective controls.

L16 ANSWER 6 OF 8 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1998209757 EMBASE

TITLE: The treatment of advanced renal cell carcinoma. Current and

prospective views.

AUTHOR: Polyzos A.; Kostakis A.

CORPORATE SOURCE: A. Polyzos, Internal Med. 1st Propedeutic Dept., General Hospital 'Laikon', GR-115 27 Athens, Greece

SOURCE: Archives of Hellenic Medicine, (1997) 14/6 (609-618).  
Refs: 55

ISSN: 1105-3992 CODEN: AEIAF7

COUNTRY: Greece

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 006 Internal Medicine  
016 Cancer  
028 Urology and Nephrology  
037 Drug Literature Index  
038 Adverse Reactions Titles

LANGUAGE: Greek

SUMMARY LANGUAGE: English; Greek

AB The natural history of renal cell carcinoma (RCC) is disappointing. Metastatic disease is present in 1/3 of patients on diagnosis while 30-40%

will develop metastases subsequently. Nephrectomy can improve quality of life even in cases with metastasis, and if combined with metastasectomy may lead to prolongation of life. Radiotherapy has a limited role in the treatment of the primary tumor because of the tumor's relative resistance and the vicinity of the spinal cord. Radiotherapy may be applied as a palliative treatment for metastatic disease. Since RCC is usually advanced,

systemic treatment is required but it is a chemoresistant tumor due mainly

to the inherent multi-drug resistance mechanics. Chemotherapeutic responses to single agents and drug combinations are disappointing, with the exception of vinblastine and floxuridine which may include low rate responses. In addition, according to the new response criteria, RCC is considered hormonally refractory, since progestins and other hormones can

neither induce responses nor improve the patient's quality of life. The best treatment responses have been achieved with biologic treatment, particularly with interferon- $\alpha$  (INF- $\alpha$ .) and interleukin-2 (IL-2). RCC

responds to IFN- $\alpha$  at a range of 15-17% with 2% complete responses. Median survival in responders in 7-18+ months (almost double that of comparative groups without treatment). INF- $\alpha$  may be administered subcutaneously,

intramuscularly or intravenously, 3-time weekly in dosages of from 1 x 10<sup>6</sup>

to 10 x 10<sup>6</sup> UT. INF- $\alpha$  has been administered in combination with chemotherapy, but conflicting results have been reported. The effects of interferon- $\beta$  and interferon- $\gamma$  have been studied in RCC, but were found to be inferior to that of INF- $\alpha$ . IL-2 has been administered intravenously in a dose of 25 MIU/m<sup>2</sup>/8 hours producing a 20% response

rate with 7% complete responses. The toxicity was significant due mainly to capillary leak syndrome. Smaller doses of IL-2 are followed by lower responses, but with no significant difference in survival. The subcutaneous administration of IL-2 carries lower toxicity but also a lower response. The co-administration of IL-2 with INF- $\alpha$  achieved a 38% response rate, but was followed by serious cardiac, hepatic and psychiatric complications. In the most recent studies the above two cytokines were combined with fluorouracil to produce response rates as high as 24-49%, but confirmatory studies are required. The present consensus is that IL-2 combinations are no better than single drug administration which yields 15-20% response rates with long-term remissions in 1/3 of patients who can be considered cured. The newer treatments are based on adoptive cellular immunotherapy either with patient's peripheral lymphocytes or tumor infiltrating lymphocytes which can be induced in vitro with IL-2 and re-administered to the patients. Another type of adoptive treatment is the administration of

\*\*\*bispecific\*\*\* monoclonal antibodies where the one site is linked to a

cancer cell while the other carries an immunocyte. The newest therapeutic modalities which have been applied in RCC are gene therapy and cancer

\*\*\*cell\*\*\* \*\*\*vaccines\*\*\*. In gene therapy, genetic material from cytokines is induced either into tumor cells or into cytotoxic lymphocytes. In both cases a significant amount of cytokines is concentrated in the tumor site. The use of cancer \*\*\*cell\*\*\*

\*\*\*vaccines\*\*\* with irradiated either autologous or allogeneic tumor

cells is being studied in phase I and II and the preliminary results seem to be encouraging.

L16 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1997:137621 CAPLUS  
DOCUMENT NUMBER: 126:184827  
TITLE: Idiotypic vaccination strategies against a murine B-cell lymphoma: dendritic cells loaded with idiotypic and \*\*\*bispecific\*\*\* idiotypic .times. anti-class II antibodies can protect against tumor growth  
AUTHOR(S): Bohlen, Herbert; Thielemann, Kris; Tesch, Hans; Engert, Andreas; Wolf, H. Juergen; Van Camp, Ben; Urbain, Jacques; Diehl, Volker  
CORPORATE SOURCE: Klinik I fur Innere Medizin, Universitat zu Koln, Koln, 50924, Germany  
SOURCE: Cytokines Mol. Ther. (1996), 2(4), 231-238  
CODEN: CMTHFP; ISSN: 1355-6568  
PUBLISHER: Martin Dunitz Ltd.  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Three strategies were used to evaluate 38C13 B-cell lymphoma-specific idiotypic immunization to protect against subsequent lymphoma challenge in C3H/He mice. It was observed that tumor-specific immunity could be induced by immunization with (i) KLH-conjugated 38C13 B-cell lymphoma idiotypic in complete Freund's adjuvants (survival rate 80%), (ii) dendritic cells pulsed in vitro with native idiotypic protein (survival rate 80%), and (iii) \*\*\*bispecific\*\*\* antibodies composed of B-lymphoma-related idiotypic and an MHC class II binding moiety (survival rate 40%). Presentation of idiotypic determinants by dendritic cells of \*\*\*bispecific\*\*\* antibody resulted in lymphoma-specific immunity and obviated the requirement for carrier protein or adjuvant. Moreover, primed dendritic cells induced predominant development of a tumor-specific T-cell response. Each of these immunization strategies resulted in long-term survival without the emergence of idiotypic variants or the induction of tumor dormancy.

L16 ANSWER 8 OF 8 MEDLINE

DUPLICATE 5

ACCESSION NUMBER: 97154859 MEDLINE  
DOCUMENT NUMBER: 97154859  
TITLE: Immunogenicity increase of autologous tumor \*\*\*cell\*\*\* \*\*\*vaccines\*\*\* by virus infection and attachment of \*\*\*bispecific\*\*\* antibodies.  
AUTHOR: Haas C; Schirmacher V  
CORPORATE SOURCE: German Cancer Research Center, Tumor Immunology, Program (0710), Heidelberg, Germany.  
SOURCE: CANCER IMMUNOLOGY, IMMUNOTHERAPY, (1996 Nov) 43 (3) 190-4. Ref: 41  
Journal code: CN3. ISSN: 0340-7004.  
PUB. COUNTRY: GERMANY: Germany, Federal Republic of  
Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals; Cancer Journals  
ENTRY MONTH: 199704  
ENTRY WEEK: 19970403

AB A new type of cancer vaccine for therapeutic application in cancer patients is described. It consists of three components. (1) autologous tumor cells, (2) Newcastle Disease Virus (NDV), to be used for infection

and (3) \*\*\*bispecific\*\*\* antibodies (bsAb) which attach to the viral hemagglutinin neuraminidase (HN) molecule on the infected tumor cells. A standardized procedure has been developed for generating virus infected human autologous tumor \*\*\*cell\*\*\* \*\*\*vaccines\*\*\* (ATV-NDV) which includes cell dissociation, removal of leukocytes and cell debris, gamma-irradiation and cryopreservation. Infection with the non-virulent strain NDV Ulster is performed within 30 min of co-incubation. While virus

infection already increased immunogenicity of the tumor vaccine, further augmentation of T cell stimulatory capacity is achieved by attachment of specially designed bi-specific antibodies (bs HN x CD28 or bs HN x CD3).

L8 ANSWER 1 OF 25 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 2000:227691 CAPLUS

DOCUMENT NUMBER: 132:250020

TITLE: \*\*\*Bispecific\*\*\* and \*\*\*trispecific\*\*\* antibodies which specifically react with inducible surface antigens as operational target structures

INVENTOR(S): \*\*\*Lindhofer, Horst\*\*\*

PATENT ASSIGNEE(S): Germany

SOURCE: PCT Int. Appl., 60 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000018806	A1	20000406	WO 1999-EP7095	19990922
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
DE 19859110	A1	20000413	DE 1998-19859110	19981221
PRIORITY APPLN. INFO.:			DE 1998-19844157	19980925
			DE 1998-19859110	19981221

AB According to the invention, an intact \*\*\*bispecific\*\*\* or \*\*\*trispecific\*\*\* antibody is provided which comprises at least the following properties: (a) binding to a T cell; (b) binding to at least one antigen on a target cell; (c) binding by the Fc portion thereof (in \*\*\*bispecific\*\*\* antibodies) or by a third specificity (in \*\*\*trispecific\*\*\* antibodies). The antigen can be induced and is not found on the target cell in a non-induced state (normal state) or it exists in a low no. that is insufficient to destroy the target cell. The use of these antibodies for immunotherapy of tumors and infections is discussed.

L8 ANSWER 2 OF 25 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 1

ACCESSION NUMBER: 1999:510768 BIOSIS

DOCUMENT NUMBER: PREV199900510768

TITLE: Method for producing heterologous bi-specific antibodies.

AUTHOR(S): \*\*\*Lindhofer, Horst (1)\*\*\* ; Thierfelder, Stephan

CORPORATE SOURCE: (1) Munchen West Germany

ASSIGNEE: GSF--Forschungszentrumfur Umweltund Gesundheit

PATENT INFORMATION: US 5945311 Aug. 31, 1999

SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Aug. 31, 1999) Vol. 1225, No. 5, pp. NO



PAGINATION.  
ISSN: 0098-1133.

DOCUMENT TYPE: Patent  
LANGUAGE: English

L8 ANSWER 3 OF 25 MEDLINE DUPLICATE 2

ACCESSION NUMBER: 1999355457 MEDLINE

DOCUMENT NUMBER: 99355457

TITLE: \*\*\*Bispecific\*\*\* antibody fragments with CD20 X CD28 specificity allow effective autologous and allogeneic T-cell activation against malignant cells in peripheral blood and bone marrow cultures from patients with B-cell lineage leukemia and lymphoma.

AUTHOR: Brandl M; Grosse-Hovest L; Holler E; \*\*\*Kolb H J\*\*\* ; Jung G

CORPORATE SOURCE: Department of Hematology and Medical Oncology, Klinikum Grosshadern, University of Munich, Germany.

SOURCE: EXPERIMENTAL HEMATOLOGY, (1999 Aug) 27 (8) 1264-70.

Journal code: EPR. ISSN: 0301-472X.

PUB. COUNTRY: Netherlands

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 199910

ENTRY WEEK: 19991003

AB \*\*\*Bispecific\*\*\* antibodies directed against tumor-associated target antigens and to surface receptors mediating T-cell activation, such as the

TCR/CD3 complex and the costimulatory receptor CD28, are capable of mediating T-cell activation resulting in tumor cell killing. In this study, we used the B-cell-associated antigens CD19 and CD20 as target structures on human leukemic cells. We found that a combination of \*\*\*bispecific\*\*\* antibody fragments (bsFab2) with target x CD3 and target x CD28 specificity induces vigorous autologous T-cell activation and killing of malignant cells in peripheral blood and bone marrow cultures from patients with chronic lymphocytic leukemia and follicular lymphoma. The bsFab2 targeting CD20 were considerably more effective than those binding to CD19. The colony-forming capacity of treated bone marrow was impaired due to large amounts of tumor necrosis factor alpha produced during bsFab2-induced T-cell activation. Neutralizing tumor necrosis factor alpha antibodies were found to reverse this negative effect without

affecting T-cell activation and tumor cell killing. CD20 x CD28 bsFab2, when used alone rather than in combination, markedly improved the recognition of leukemic cells by allogeneic T cells. Therefore, these reagents may be capable of enhancing the immunogenicity of leukemic cells in general and, in particular, of increasing the antileukemic activity of allogeneic donor buffy coat cells in relapsed bone marrow transplanted patients.

L8 ANSWER 4 OF 25 MEDLINE

DUPLICATE 3

ACCESSION NUMBER: 1999343730 MEDLINE

DOCUMENT NUMBER: 99343730

TITLE: Simultaneous activation of T cells and accessory cells by a

new class of intact \*\*\*bispecific\*\*\* antibody results in efficient tumor cell killing.

AUTHOR: \*\*\*Zeidler R\*\*\* ; Reisbach G; Wollenberg B; Lang S; Chaubal S; Schmitt B; \*\*\*Lindhofer H\*\*\*

CORPORATE SOURCE: Clinical Cooperation Group Bispecific Antibodies,

Department of Otorhinolaryngology, Ludwig-Maximilians-University, Munich, Germany.  
SOURCE: JOURNAL OF IMMUNOLOGY, (1999 Aug 1) 163 (3) 1246-52.  
Journal code: IFB. ISSN: 0022-1767.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals  
ENTRY MONTH: 199910  
ENTRY WEEK: 19991002

AB \*\*\*Bispecific\*\*\* Abs (bsAb) are promising immunological tools for the elimination of tumor cells in minimal residual disease situations. In principle, they target an Ag on tumor cells and recruit one class of effector cell. Because immune reactions in vivo are more complex and are mediated by different classes of effector cell, we argue that conventional bsAb might not yield optimal immune responses at the tumor site. We therefore constructed a bsAb that combines the two potent effector subclasses mouse IgG2a and rat IgG2b. This \*\*\*bispecific\*\*\* molecule not only recruits T cells via its one binding arm, but simultaneously activates FcγR+ accessory cells via its Fc region. We demonstrate here that the activation of both T lymphocytes and accessory cells leads to production of immunomodulating cytokines like IL-1β, IL-2, IL-6, IL-12, and DC-CK1. Thus this new class of bsAb elicits excellent antitumor activity in vitro even without the addition of exogenous IL-2, and therefore represents a totally self-supporting system.

L8 ANSWER 5 OF 25 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.  
ACCESSION NUMBER: 1999316170 EMBASE  
TITLE: [Adoptive transfer of malignoma reactive T cells].  
ADOPTIVER TRANSFER VON MALIGNOMREAKTIVEN T-ZELLEN.  
AUTHOR: Bernhard H.; Meyer zum Buschenfelde Ch.; \*\*\*Kolb H.-J.\*\*\*  
; Peschel Ch.  
CORPORATE SOURCE: Dr. H. Bernhard, III. Medizinische Klinik, Klinikum rechts der Isar, Technische Universität München,  
Ismaningerstrasse 22, D-81644 München, Germany. helga.bernhard@tum.ce  
SOURCE: Onkologe, (1999) 5/8 (688-694).  
Refs: 28  
ISSN: 0947-8965 CODEN: ONKOF4  
COUNTRY: Germany  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 016 Cancer  
026 Immunology, Serology and Transplantation  
LANGUAGE: German

L8 ANSWER 6 OF 25 BIOSIS COPYRIGHT 2000 BIOSIS  
ACCESSION NUMBER: 2000:43330 BIOSIS  
DOCUMENT NUMBER: PREV200000043330  
TITLE: The generation of monospecific and \*\*\*bispecific\*\*\* anti-viral cytotoxic T lymphocytes (CTL) for the prophylaxis of patients receiving an allogeneic BMT.  
AUTHOR(S): Regn, S. (1); Chen, X. (1); \*\*\*Kolb, H.-J. (1)\*\*\* ;  
Roskrow, M. (1)  
CORPORATE SOURCE: (1) GSF (National Research Centre for Environment and Health) and Medical Clinic III, Grosshadern University of

SOURCE: Munich, Munich Germany  
Blood, (Nov. 15, 1999) Vol. 94, No. 10 SUPPL. 1 PART 1,  
pp. 154a.  
Meeting Info.: Forty-first Annual Meeting of the American  
Society of Hematology New Orleans, Louisiana, USA December  
3-7, 1999 The American Society of Hematology  
. ISSN: 0006-4971.  
DOCUMENT TYPE: Conference  
LANGUAGE: English

L8 ANSWER 7 OF 25 MEDLINE DUPLICATE 4  
ACCESSION NUMBER: 1999380234 MEDLINE  
DOCUMENT NUMBER: 99380234  
TITLE: Gene therapy of B-cell lymphoma with cytokine gene-  
modified trioma cells.  
AUTHOR: Strehl J; Selmayr M; Kremer J P; Hultner L;  
\*\*\*Lindhofer\*\*\*  
\*\*\* H\*\*\* ; Mocikat R  
CORPORATE SOURCE: GSF-Institut fur Molekulare Immunologie, Munich, Germany.  
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1999 Sep 24) 83 (1)  
113-20.  
Journal code: GQU. ISSN: 0020-7136.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals; Cancer Journals  
ENTRY MONTH: 199911  
ENTRY WEEK: 19991104

AB The trioma approach is a new immunotherapeutic strategy for treating  
B-cell lymphomas. It is based on converting the tumour idiotype to a  
\*\*\*bispecific\*\*\* immunoglobulin that redirects the idiotype to  
antigen-presenting cells. We show here that even pre-existing tumours can  
be eradicated by trioma vaccination, that the trioma approach is superior  
to vaccination with cytokine gene-modified autologous tumour cells and  
that there is a synergism between trioma immunisation and GM-CSF gene  
transfer. Furthermore, we show that the immunising potential of GM-CSF  
gene-modified autologous lymphoma cells is not as dependent on the  
cytokine expression level as described for other tumour models, such that  
even minute expression rates are effective. IL-4 gene transfer in the  
lymphoma model is considerably less efficient or even ineffective when  
more sensitive systems are used. Remarkably, trioma-mediated effects are  
extinguished when IL-4 is expressed by the trioma cell. Copyright 1999  
Wiley-Liss, Inc.

L8 ANSWER 8 OF 25 CAPLUS COPYRIGHT 2000 ACS  
ACCESSION NUMBER: 1999:12374 CAPLUS  
DOCUMENT NUMBER: 130:51356  
TITLE: Method of ex vivo immunizing using heterologous  
intact \*\*\*bispecific\*\*\* and/or \*\*\*trispecific\*\*\*  
antibodies  
INVENTOR(S): \*\*\*Lindhofer, Horst\*\*\* ; Kolb, Hans-Jochem;  
\*\*\*Zeidler, Reinhard\*\*\* ; \*\*\*Bornkamm, Georg\*\*\*  
PATENT ASSIGNEE(S): Gsf-Forschungszentrum Fur Umwelt Und Gesundheit,  
GmbH,  
Germany  
SOURCE: Eur. Pat. Appl., 19 pp.  
CODEN: EPXXDW

DOCUMENT TYPE: Patent  
LANGUAGE: German  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 885614	A2	19981223	EP 1998-110972	19980616
EP 885614	A3	19990113		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
DE 19725586	A1	19981224	DE 1997-19725586	19970617
DE 19725586	C2	19990624		
JP 11071288	A2	19990316	JP 1998-170389	19980617
PRIORITY APPLN. INFO.: DE 1997-19725586 19970617				
AB The invention describes a method for ex vivo immunization of human and animal with the following steps: (a) isolation of autologous tumor cells; (b) treatment of tumor cells to prevent their survival after reinfusion; (c) incubation of treated tumor cells with intact heterologous ***bispecific*** and or ***trispecific*** antibodies. The antibodies have the following properties: binding to T-cells, binding to an antigen from the tumor cells, binding through its Fc fragment (by ***bispecific*** antibodies) or through a third specificity (by ***trispecific*** antibodies) to Fc-pos. cells.				

L8 ANSWER 9 OF 25 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1998:176147 CAPLUS

DOCUMENT NUMBER: 128:216369

TITLE: Bi- and \*\*\*trispecific\*\*\* antibodies for induction

of tumor immunity

INVENTOR(S): \*\*\*Lindhofer, Horst\*\*\* ; Kolb, Hans-Jochem; Thierfelder, Stefan

PATENT ASSIGNEE(S): GSF-Forschungszentrum fuer Umwelt und Gesundheit G.m.b.H. Neuherberg, Germany

SOURCE: Ger. Offen., 18 pp.

CODEN: GWXXBX

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19710497	A1	19980305	DE 1997-19710497	19970313
DE 19710497	C2	19980709		
DE 19649223	A1	19980305	DE 1996-19649223	19961127
DE 19649223	C2	19980730		
EP 826696	A1	19980304	EP 1997-115190	19970902
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EP 826695	A1	19980304	EP 1997-115188	19970902
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 10179151	A2	19980707	JP 1997-238745	19970903
US 5985276	A	19991116	US 1997-922966	19970903
PRIORITY APPLN. INFO.: DE 1996-19635743 19960903				
DE 1996-19648976 19961126				
DE 1996-19649223 19961127				
DE 1997-19710497 19970313				

AB The invention concerns intact \*\*\*bispecific\*\*\* or \*\*\*trispecific\*\*\* antibodies, which can bind simultaneously to the T-cell receptor complex of T-cells, to tumor-assocd. antigens of a tumor cell, and through the Fc fragment of \*\*\*bispecific\*\*\* antibodies to Fc-receptor pos. cells. The use of these antibodies for induction of tumor immunity in humans and animals is discussed.

L8 ANSWER 10 OF 25 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1998:150437 BIOSIS

DOCUMENT NUMBER: PREV199800150437

TITLE: A \*\*\*bispecific\*\*\* antibody induces efficient killing of tumor cells: Phase I-trial in patients with HNSCC.

AUTHOR(S): Wollenberg, B. (1); Schmitt, B. (1); Erndl, S.; Lang, S. (1); \*\*\*Lindhofer, H.\*\*\* ; Kastenbauer, E. (1); \*\*\*Zeidler, R. (1)\*\*\*

CORPORATE SOURCE: (1) Dep. ENT, LMU, Munich Germany

SOURCE: British Journal of Cancer, (1998) Vol. 77, No. SUPPL. 1, pp. 46.

Meeting Info.: International Symposium on Metastases in Head and Neck Cancer Kiel, Germany January 15-18, 1998

ISSN: 0007-0920.

DOCUMENT TYPE: Conference

LANGUAGE: English

L8 ANSWER 11 OF 25 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.DUPLICATE 5

ACCESSION NUMBER: 1998168459 EMBASE

TITLE: CD22 is a suitable target molecule for detection and high-dose, myeloablative radioimmunotherapy with the monoclonal antibody LL2 in acute lymphatic leukaemia and Waldenstrom's macroglobulinaemia.

AUTHOR: Behr T.M.; Holler E.; Gratz S.; Wormann B.; Sharkey R.M.; Dunn R.M.; Hiddemann W.; \*\*\*Kolb H.-J.\*\*\* ; Goldenberg D.M.; Becker W.

CORPORATE SOURCE: T.M. Behr, Department of Nuclear Medicine, Georg-August-University of Gottingen, Robert-Koch Str. 40, D-37075 Gottingen, Germany

SOURCE: Tumor Targeting, (1998) 3/1 (32-40).

Refs: 19

ISSN: 1351-8488 CODEN: TUTAF

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 006 Internal Medicine

014 Radiology

025 Hematology

030 Pharmacology

037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB CD22 is a 135-kD glycoprotein of the immunoglobulin superfamily which is expressed on most B lymphocytes. It has been used successfully as a target

molecule for radioimmunodetection and therapy of B-cell non-Hodgkin's lymphoma with the monoclonal antibody CD22 (Mab), LL2. Since CD22 is highly expressed on blasts in acute lymphatic leukaemia of B-cell origin as well as on the malignant lymphocytes of macroglobulinaemia, we studied the potential of LL2 for the detection and therapy of these two haematological malignancies in two pilot cases. A 43-year-old male suffered from macroglobulinaemia, first diagnosed 4 years earlier. The

IgM

produced by the malignant clone cross-reacted with a ganglioside of

peripheral neurons, causing severe and progressive sensomotor neuropathy. Several bone marrow biopsies as well as a splenectomy were not able to demonstrate the presence of a malignant clone which would be responsible for the IgM production. A localised tumour was suspected, but was not detected by any radiological procedure. Thus, the patient underwent radioimmunodetection (RAID) with 99mTc-LL2 Fab1 (LymphoScan(TM)). The second patient was a 28-year-old male who had common acute lymphatic leukaemia (c-ALL) for 8 years. He had failed 6 high-dose chemotherapy regimens with allogenic bone marrow or stem cell transplantations from

his

HLA-compatible brother. The patient had also failed two immunotherapeutic approaches with \*\*\*bispecific\*\*\* murine antibodies, which had caused high titres of HAMA. The patient was treated, with high-dose radioimmunotherapy with 131I-labelled humanised LL2 IgG in myeloablative intention with stem cell support. Although all diagnostic procedures had failed in the macroglobulinaemia patient, 99mTc-LL2 Fab1 showed excellent targeting of widespread parailiac, mediastinal, axillary and cervical lymph node involvement (all smaller than 1 cm in size) as well as a

patchy

uptake all over the patient's bone marrow as a sign of generalised tumour infiltration, precluding any localised treatment approach, such as external beam irradiation. The c-ALL patient underwent a diagnostic study with humanised LL2 (50 mg of protein, 8 mCi 131I) in order to assess tumour targeting and dosimetry, and was treated based on the result, with 258 mCi hLL2 at the same protein dose. Strong uptake occurred in the patient's bone marrow as well as in several extramedullary tumour sites (lymph nodes, spleen, muscular infiltration of the thigh). At a marrow dose of 30 Gy (whole-body 3.5 Gy, lung 12 Gy), the patient went into complete remission and bone marrow aplasia within two days. Reingraftment of the red marrow took place rapidly. The patient experienced a complete remission lasting for 7 weeks. Relapsed ALL and Waldenstrom's macroglobulinaemia seem to be suitable targets for a radioimmunotherapeutic approach with the anti-CD22 monoclonal antibody, LL2. Future studies will show whether high-dose RAIT with heterologous stem cell support may be able to induce longer-lasting remissions or even be curative in these haematologic malignancies.

L8 ANSWER 12 OF 25 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1997:649115 CAPLUS

DOCUMENT NUMBER: 127:277199

TITLE: Hybridomas of malignant B-cells and antigen presenting

cells for use in stimulating an immune response to B-cell neoplasms

INVENTOR(S): Mocikat, Ralf; \*\*\*Lindhofer, Horst\*\*\* ; Thierfelder, Stefan

PATENT ASSIGNEE(S): GSF - Forschungszentrum fuer Umwelt und Gesundheit GmbH, Germany

SOURCE: Ger., 6 pp. CODEN: GWXXAW

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19634159	C1	19970925	DE 1996-19634159	19960823
EP 825256	A2	19980225	EP 1997-113697	19970807

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,

IE, FI  
 JP 10155483 A2 19980616 JP 1997-228536 19970825  
 US 6007807 A 19991228 US 1997-917216 19970825  
 PRIORITY APPLN. INFO.: DE 1996-19634159 19960823  
 AB Hybridomas of malignant B-cells and antigen presenting cells that present bi-specific antibodies to tumor-specific antigens and the cell surface antigens of antigen-presenting cells are described for use in the treatment of B-lymphomas. These hybridomas lead to the formation of tumor-specific T cells. The B-cells are preferably not human (mouse or rat) and the hybridomas are quickly recognized as foreign when injected into the host.

L8 ANSWER 13 OF 25 MEDLINE DUPLICATE 6  
 ACCESSION NUMBER: 97336010 MEDLINE  
 DOCUMENT NUMBER: 97336010  
 TITLE: Trioma-based vaccination against B-cell lymphoma confers long-lasting tumor immunity.  
 AUTHOR: Mocikat R; Selmayr M; Thierfelder S; \*\*\*Lindhofer H\*\*\*  
 CORPORATE SOURCE: GSF-Institut fur Immunologie, Munchen, Germany..  
 mocikat@gsf.de  
 SOURCE: CANCER RESEARCH, (1997 Jun 15) 57 (12) 2346-9.  
 Journal code: CNF. ISSN: 0008-5472.  
 PUB. COUNTRY: United States  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals; Cancer Journals  
 ENTRY MONTH: 199709  
 ENTRY WEEK: 19970903  
 AB A major goal of tumor immunotherapy is the induction of a systemic immune response against tumor antigens such as the tumor-specific immunoglobulin idiotype (Id) expressed by lymphomas of the B-cell lineage. We describe an approach based on specific redirection of the tumor Id toward professional antigen-presenting cells (APCs), thereby overcoming the inefficient presentation on the parental transformed B cell. Lymphoma cells are fused to a xenogeneic hybridoma cell line that secretes an antibody against a surface molecule on APCs. Due to preferential assembly between heavy and light chains of antibodies of different species-origin, the resulting "trioma" cells produce at high yield a \*\*\*bispecific\*\*\* antibody containing the lymphoma Id and the APC-binding arm, which redirects the Id to APCs. Processing and presentation of the Id will lead to T-cell activation. An absolute requirement for inducing a complete tumor protection was the immunization with antibody-secreting trioma cells as a cell-based vaccine instead of the soluble \*\*\*bispecific\*\*\* antibody. Tumor immunity was specific and long-lasting. Both CD4+ and CD8+ T cells were necessary for inducing tumor immunity.

L8 ANSWER 14 OF 25 BIOSIS COPYRIGHT 2000 BIOSIS  
 ACCESSION NUMBER: 1997:426558 BIOSIS  
 DOCUMENT NUMBER: PREV199799725761  
 TITLE: \*\*\*Bispecific\*\*\* antibodies effectively purge cancer cells from peripheral blood stem cell collections without affecting colony forming units.  
 AUTHOR(S): \*\*\*Lindhofer, H.\*\*\* ; Menzel, H.; Zengerle, U.;  
 \*\*\*Zeidler, R.\*\*\* ; Chaubal, S.; \*\*\*Kolb, H. J.\*\*\* ;  
 Thierfelder, S.  
 CORPORATE SOURCE: GSF Inst. Immunol., Munchen Med. III Klinikum, Grosshadern Germany

SOURCE: Experimental Hematology (Charlottesville), (1997) Vol. 25,  
No. 8, pp. 879.  
Meeting Info.: 26th Annual Meeting of the International  
Society for Experimental Hematology Cannes, France August  
24-28, 1997  
ISSN: 0301-472X.  
DOCUMENT TYPE: Conference; Abstract  
LANGUAGE: English

L8 ANSWER 15 OF 25 BIOSIS COPYRIGHT 2000 BIOSIS  
ACCESSION NUMBER: 1997:230396 BIOSIS  
DOCUMENT NUMBER: PREV199799529599  
TITLE: An intact \*\*\*bispecific\*\*\* antibody induces activation  
of T-cells and monocytes/macrophages resulting in  
efficient  
killing of tumor cells.  
AUTHOR(S): \*\*\*Zeidler, R.\*\*\* ; Schmitt, B.; Erndl, S.; Lang, S.;  
Wollenberg, B.; Lindofer, H.  
CORPORATE SOURCE: Dep. Otorhinolaryngology, Ludwig-Maximilians-Univ.,  
Marchioninstr. 15, D-81377 Munich Germany  
SOURCE: Proceedings of the American Association for Cancer  
Research  
Annual Meeting, (1997) Vol. 38, No. 0, pp. 29.  
Meeting Info.: Eighty-eighth Annual Meeting of the  
American  
Association for Cancer Research San Diego, California, USA  
April 12-16, 1997  
ISSN: 0197-016X.  
DOCUMENT TYPE: Conference; Abstract  
LANGUAGE: English

L8 ANSWER 16 OF 25 MEDLINE DUPLICATE 7  
ACCESSION NUMBER: 97131784 MEDLINE  
DOCUMENT NUMBER: 97131784  
TITLE: \*\*\*Bispecific\*\*\* antibodies target operationally  
tumor-specific antigens in two leukemia relapse models.  
AUTHOR: \*\*\*Lindhofer H\*\*\* ; Menzel H; Gunther W; Hultner L;  
Thierfelder S  
CORPORATE SOURCE: Forschungszentrum für Umwelt und Gesundheit (GSF)-Institut  
für Immunologie, Munich, Germany.  
SOURCE: BLOOD, (1996 Dec 15) 88 (12) 4651-8.  
Journal code: A8G. ISSN: 0006-4971.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer  
Journals  
ENTRY MONTH: 199704  
ENTRY WEEK: 19970402

AB Despite improved procedures in chemotherapy and bone marrow  
transplantation (BMT), post-BMT leukemia relapse rates have remained  
rather constant in the last decade. Immunotherapy with monoclonal or  
\*\*\*bispecific\*\*\* antibodies (bsAb) is a promising approach to improve  
this situation, but is hampered by the absence of tumor-specific antigens  
on the majority of tumors. To evade this problem, we developed a new  
tumor-specific approach in which \*\*\*bispecific\*\*\* antibodies exploit  
chimerism after allogeneic BMT by redirecting donor T cells against  
recipient-specific antigens on tumor cells. Two different leukemia  
relapse  
models were established using a T-cell lymphoma (ST-1) and a B-cell



lymphoma (BCL1) to evaluate the efficiency of such a therapy. In these experiments, irradiated BALB/c (Thy-1.2+, I-Ad) mice were transplanted with C57BL/6 Thy-1.1 (I-Ab) BM cells under the protection of graft-versus-host disease-preventing monoclonal antibodies. Forty-five days after BMT, the chimeric mice were injected with either 2 x 10<sup>4</sup> recipient-type, Thy-1.2+, CD3- ST-1 cells or major histocompatibility complex (MHC) class II+ (I-Ad)-BCL1 cells. Four days later, the mice were treated with 8 microg bsAb G2 (anti-CD3 x anti-Thy-1.2) or 10 microg (+10 microg, day 6) bsAb BiC (anti-CD3 x anti-I-Ad), respectively. These combinations guaranteed exclusive binding of the bsAbs target arms to tumor cells, leaving the surrounding, donor-type hematopoietic cells unbound. Compared with the parental antibodies, the bsAbs markedly reduced tumor mortality. Between 34% and 83% of mice survived in the bsAb groups compared with 0% of the control groups treated with parental antibodies, clearly documenting the benefit of the redirection principle. Furthermore, cytokine release (interleukin-6) after anti-CD3 antibody or bsAb treatment was decreased by administering a low-dose antibody preinjection. We have shown (1) that 6 weeks after BMT, when donor T-cell reconstitution is still in progress, T-cell-redirecting bsAb are clearly superior to parental antibodies in terms of tumor cell elimination; and (2) that the polymorphism of a common antigen such as Thy-1 or a clinically more relevant target antigen such as MHC class II can be used as an operational tumor-specific antigen after allogeneic BMT.

L8 ANSWER 17 OF 25 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1996:450856 BIOSIS

DOCUMENT NUMBER: PREV199699173212

TITLE: Increased tumor-specificity and -elimination by selectively

binding \*\*\*bispecific\*\*\* antibodies in vivo.

AUTHOR(S): \*\*\*Lindhofer, H.\*\*\* ; Mysliwietz, J.; Thierfelder, S.

CORPORATE SOURCE: GSF-Inst. Immunol., Muenchen Germany

SOURCE: Experimental Hematology (Charlottesville), (1996) Vol. 24, No. 9, pp. 1090.

Meeting Info.: 25th Annual Meeting of the International Society for Experimental Hematology New York, New York,

USA

August 23-27, 1996

ISSN: 0301-472X.

DOCUMENT TYPE: Conference

LANGUAGE: English

L8 ANSWER 18 OF 25 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1995:498513 CAPLUS

DOCUMENT NUMBER: 122:237782

TITLE: Process for producing heterologous \*\*\*bispecific\*\*\* antibodies

INVENTOR(S): \*\*\*Lindhofer, Horst\*\*\* ; Thierfelder, Stefan

PATENT ASSIGNEE(S): GSF = Forschungszentrum fuer Umwelt und gesundheit GmbH, Germany

SOURCE: Ger., 10 pp.  
CODEN: GWXXAW

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4419399	C1	19950309	DE 1994-4419399	19940603
WO 9533844	A1	19951214	WO 1995-EP1850	19950516
W: CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 763128	A1	19970319	EP 1995-919458	19950516
EP 763128	B1	19991201		
R: AT, BE, CH, DE, DK, FR, GB, IT, LI, NL, SE				
JP 09506001	T2	19970617	JP 1995-500228	19950516
AT 187176	E	19991215	AT 1995-919458	19950516
US 5945311	A	19990831	US 1996-758430	19961129
PRIORITY APPLN. INFO.:			DE 1994-4419399	19940603
			WO 1995-EP1850	19950516

AB A process is described for producing heterologous \*\*\*bispecific\*\*\*  
IgG  
antibodies, or quadromas, from 2 fused hybridomas. One of the hybridomas  
produces antibodies with an affinity for protein A, and the other  
antibodies with little or no affinity for protein A. Thus, a quadroma  
was produced which included an anti-mouse CD3 rat antibody of the IgG2b  
subclass, and an anti-mouse Thy-1.2 mouse antibody of the IgG2a subclass.

L8 ANSWER 19 OF 25 MEDLINE DUPLICATE 8  
ACCESSION NUMBER: 95394030 MEDLINE  
DOCUMENT NUMBER: 95394030  
TITLE: Immunosuppression by Fc region-mismatched anti-T cell  
antibody treatment.  
AUTHOR: Thierfelder S; Mocikat R; Mysliwietz J; \*\*\*Lindhofer  
H\*\*\*  
; Kremmer E  
CORPORATE SOURCE: GSF-Forschungszentrum fur Umwelt und Gesundheit, Institut  
fur Immunologie, Munich, Germany..  
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1995 Aug) 25 (8) 2242-6.  
Journal code: EN5. ISSN: 0014-2980.  
PUB. COUNTRY: GERMANY: Germany, Federal Republic of  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals; Cancer Journals  
ENTRY MONTH: 199512

AB Formation of anti-antibodies (anti-Ab) is known to counteract  
immunotherapy with anti-T cell antibodies. Our previously described  
immunological approach prevented anti-Ab with the consequence of  
prolonged survival of fully mismatched skin grafts in C57BL/6 mice. These mice were  
treated with a single priming injection of a monoclonal anti-T cell Ab  
followed by repeated injections of anti-T cell mAb differing in species  
origin from the priming mAb. We now show prolonged tolerance to  
discordant xenogeneic, to \*\*\*bispecific\*\*\*, and even to polyclonal Ab, and  
demonstrate that the underlying immunosuppressive principle is due to a  
difference in heavy chain constant region between first and second  
antibodies, independent of whether or not they share the same idiotype.

To examine this phenomenon, a panel of mAb was generated which share the  
same mouse anti-Thy-1.2 idiotype, but carry a human IgG1(T23), IgG3(T212C8),  
or

mouse IgG2a(MmT1) constant heavy chain region. We found that sequential injection of MmT1 and T23 according to the above treatment schedule induced huIgG1 isotype-specific tolerance to T23, which was similar to that seen when using a primary mAb (MmT5) that was, instead, fully mismatched with T23 in both idiotype and constant region. Thus, differences of idiotype between primary and booster Ab were inconsequential for their ability to inhibit anti-Ab formation. This novel form of induced specific tolerance to anti-T cell Ig survived graft rejection and was still evident 230 days after termination of the T cell depletion protocol. Taken together, these results demonstrate that rechallenge with Fc region-mismatched Ab opens an immunological window that allows for induction of tolerance to immunogenic anti-T cell Ab and prolonged immunosuppression.

L8 ANSWER 20 OF 25 BIOSIS COPYRIGHT 2000 BIOSIS  
 ACCESSION NUMBER: 1995:424064 BIOSIS  
 DOCUMENT NUMBER: PREV199598438364  
 TITLE: Leukemia relapse after aBMT: \*\*\*Bispecific\*\*\*  
 antibodies target operationally tumor-specific antigens.  
 AUTHOR(S): \*\*\*Lindhofer, H.\*\*\* ; Menzel, H.; Thierfelder, S.  
 CORPORATE SOURCE: GSF-Inst. Immunol., Muenchen Germany  
 SOURCE: Experimental Hematology (Charlottesville), (1995) Vol. 23,  
 No. 8, pp. 788.  
 Meeting Info.: 24th Annual Meeting of the International  
 Society for Experimental Hematology Duesseldorf, Germany  
 August 27-31, 1995  
 ISSN: 0301-472X.  
 DOCUMENT TYPE: Conference  
 LANGUAGE: English

L8 ANSWER 21 OF 25 BIOSIS COPYRIGHT 2000 BIOSIS  
 ACCESSION NUMBER: 1995:383349 BIOSIS  
 DOCUMENT NUMBER: PREV199598397649  
 TITLE: Generation of \*\*\*bispecific\*\*\* Ab-fragments for  
 targeting T cell mediated lysis of tumor cells in a mouse  
 lymphoma model.  
 AUTHOR(S): Bauer, Konrad (1); \*\*\*Lindhofer, Horst (1)\*\*\* ;  
 Plueckthun, Andreas; Mocikat, Ralph (1)  
 CORPORATE SOURCE: (1) GSF-Inst. Immunol., Marchionistr. 25, D-81377 Muenchen  
 Germany  
 SOURCE: 9TH INTERNATIONAL CONGRESS OF IMMUNOLOGY.. (1995) pp. 464.  
 The 9th International Congress of Immunology.  
 Publisher: 9th International Congress of Immunology San  
 Francisco, California, USA.  
 Meeting Info.: Meeting Sponsored by the American  
 Association of Immunologists and the International Union  
 of Immunological Societies San Francisco, California, USA  
 July 23-29, 1995  
 DOCUMENT TYPE: Conference  
 LANGUAGE: English

L8 ANSWER 22 OF 25 MEDLINE DUPLICATE 9  
 ACCESSION NUMBER: 95325592 MEDLINE  
 DOCUMENT NUMBER: 95325592  
 TITLE: Preferential species-restricted heavy/light chain pairing  
 in rat/mouse quadromas. Implications for a single-step  
 purification of \*\*\*bispecific\*\*\* antibodies.

AUTHOR: \*\*\*Lindhofer H\*\*\* ; Mocikat R; Steipe B; Thierfelder S  
CORPORATE SOURCE: GSF, Immunology Institute, Munich, Germany..  
SOURCE: JOURNAL OF IMMUNOLOGY, (1995 Jul 1) 155 (1) 219-25.  
Journal code: IFB. ISSN: 0022-1767.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals  
ENTRY MONTH: 199510

AB Conventional mouse/mouse or rat/rat hybrid-hybridoma supernatants contain up to 10 different IgG molecules consisting of various combinations of heavy and light chains. Hence, the yield of functional \*\*\*bispecific\*\*\* Ab is low, and purification is often complicated, hampering a general preclinical evaluation of, e.g., \*\*\*bispecific\*\*\* Ab-mediated tumor immunotherapy in animal models. In experiments to overcome this drawback we found that fusion of rat with mouse hybridomas opens the possibility of large scale production of \*\*\*bispecific\*\*\* Ab due to the increased incidence of correctly paired Ab and facilitated purification. In essence, rat/mouse quadroma-derived \*\*\*bispecific\*\*\* Ab have the following advantages: 1) enrichment of functional \*\*\*bispecific\*\*\* Ab because of preferential species-restricted heavy/light chain pairing (observed in four of four rat-mouse quadromas) in contrast to the random pairing in conventional mouse/mouse or rat/rat quadromas, and 2) a possible one-step purification of the quadroma supernatant with protein A. This simple chromatography step does not bind unwanted variants with parental rat/rat heavy chain configuration, and the desired rat/mouse \*\*\*bispecific\*\*\* Ab are retained, which can then easily be separated from parental mouse Ab by sequential pH elution.

L8 ANSWER 23 OF 25 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1995:362606 BIOSIS  
DOCUMENT NUMBER: PREV199598376906  
TITLE: Preferential species-restricted heavy/light chain pairing in rat/mouse quadromas: Implications for a single-step purification of \*\*\*bispecific\*\*\* antibodies.  
AUTHOR(S): \*\*\*Lindhofer, Horst\*\*\* ; Mocikat, Ralph; Steipe, Boris; Thierfelder, Stefan (1)  
CORPORATE SOURCE: (1) GSF-Inst. Immunologie, Marchioninistr. 25, 81377 Munich  
Germany  
SOURCE: Journal of Immunology, (1995) Vol. 155, No. 1, pp. 218-225.  
ISSN: 0022-1767.  
DOCUMENT TYPE: Article  
LANGUAGE: English

AB Conventional mouse/mouse or rat/rat hybrid-hybridoma supernatants contain up to 10 different IgG molecules consisting of various combinations of heavy and light chains. Hence, the yield of functional \*\*\*bispecific\*\*\* Ab is low, and purification is often complicated, hampering a general preclinical evaluation of, e.g., \*\*\*bispecific\*\*\* Ab-mediated tumor immunotherapy in animal models. In experiments to overcome this drawback we found that fusion of rat with mouse hybridomas opens the possibility of large scale production of \*\*\*bispecific\*\*\* Ab due to the increased incidence of correctly paired Ab and facilitated purification. In

essence,

rat/mouse quadroma-derived \*\*\*bispecific\*\*\* Ab have the following advantages: 1) enrichment of functional \*\*\*bispecific\*\*\* Ab because of

preferential species-restricted heavy/light chain pairing (observed in four of four rat-mouse quadromas) in contrast to the random pairing in conventional mouse/mouse or rat/rat quadromas, and 2) a possible one-step purification of the quadroma supernatant with protein A. This simple chromatography step does not bind unwanted variants with parental rat/rat heavy chain configuration, and the desired rat/mouse \*\*\*bispecific\*\*\* Ab are retained, which can then easily be separated from parental mouse

Ab

by sequential pH elution.

L8 ANSWER 24 OF 25 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1994:468541 BIOSIS

DOCUMENT NUMBER: PREV199497481541

TITLE: Rat-mouse quadromas allow augmented generation of \*\*\*bispecific\*\*\* antibodies and single step

purification:

First in vivo studies.

AUTHOR(S): \*\*\*Lindhofer, H.\*\*\* ; Menzel, H.; Thierfelder, S.

CORPORATE SOURCE: GSF-Inst. Immunologie, Munich Germany

SOURCE: Experimental Hematology (Charlottesville), (1994) Vol. 22, No. 8, pp. 763.

Meeting Info.: 23rd Annual Meeting of the International Society for Experimental Hematology Minneapolis,

Minnesota,

USA August 21-25, 1994

ISSN: 0301-472X.

DOCUMENT TYPE: Conference

LANGUAGE: English

L8 ANSWER 25 OF 25 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1995:47142 BIOSIS

DOCUMENT NUMBER: PREV199598061442

TITLE: Preferential species-restricted heavy/light chain pairing in rat/mouse quadromas detected during single step purification of \*\*\*bispecific\*\*\* antibodies on protein A.

AUTHOR(S): \*\*\*Lindhofer, H.\*\*\* ; Mocikat, R.; Thierfelder, S.

CORPORATE SOURCE: Inst. Immunol., Muenchen Germany

SOURCE: Immunobiology, (1994) Vol. 191, No. 2-3, pp. 248.

Meeting Info.: XXVth Meeting of the Society of Immunology Konstanz, Germany September 21-24, 1994

ISSN: 0171-2985.

DOCUMENT TYPE: Conference

LANGUAGE: English

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**Time:** 15:11

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5	L5	4	zeidler-r\$.in.
6	L6	2	bornkamm-g\$.in.
7	L7	28	3 or 4 or 5 or 6
8	L8	152	424/277.1.ccls.
9	L9	4066	autologous
10	L10	65	9 and 8
11	L13	63	424/136.1.ccls.